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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/749,630	12/31/2003	Heinz-Werner Kleemann	DEAV2002/0095 US CNT	9797

5487 7590 11/24/2006

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EXAMINER	
SEAMAN, D MARGARET M	
ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 11/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/749,630	KLEEMANN ET AL.	
	Examiner	Art Unit	
	D. Margaret Seaman	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-20,36,38,40,42,44,46 and 48-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-6,8 and 49* is/are allowed.

6)☒ Claim(s) *9-20,36,38,40,42,44,46,48 and 50-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RCE papers were filed 4/10/2006 and this application was filed 12/31/2003 which is a CON of PCT/EP03/07024 (7/2/2003). Claims 1-6, 8-20, 36, 38, 40, 42, 44, 46 and 48-64 are before the examiner.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 9-20, 36, 38, 40, 42, 44, 46, 48 and 50-64 are (remain) rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5)

the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

1) The breadth of the claims,
2) The nature of the invention,
3) The state of the prior art,
4) The level of one of ordinary skill,
5) The level of predictability in the art,
6) The amount of direction provided by the inventor,
7) The existence of working examples,
8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention: The nature of the invention is the method of treating a disorder that is modulated by the NHE-1 receptor.

The state of the prior art: The state of the prior art is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat or prevent which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. Drugs that are known to be effective against small cell lung cancer are inactive in melanoma (Sof'ina et al, Experimental Evaluation of Antitumor Drugs in the

USA and USSR and Clinical Correlation NCI Monograph 55. NIH Publication No. 80-1933 (1980), page 77)

The predictability in the art: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects of all diseases, whether or not the modulation of NHE-1 receptors would make a difference in the disease. Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in-vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic

Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Hence, in the absence of a showing of a nexus between any and all known diseases and the modulation of NHE-1 receptors, one of ordinary skill in the art is unable to fully predict possible results from the administration of the compound of claim 1 due to the unpredictability of the role of modulation of NHE-1 receptors.

The presence or absence of working examples: The compounds have been tested for inhibition of NHE-1. However, the instantly claimed compounds have not been tested for their ability to treat any specific disease/condition, including all cancers. Compound 15 has 5-position Hydrogen while compound 16 has 5-position methoxy and their activities are 0.0015 for compound 15 and 1.67 for compound 16. Compound 14 has a chlorine subsistent with 2.46 activity while

compound 13 has fluorine with 0.039 activity. Compound 16 has a cinnolin substituent with 1.67 activity as compared to compound 11 has quinoline substituent with 0.047 activity. Compound 5 has a 2-quinoline with 4.98 activity as compared to compound 6 having 4-quinoline with 0.206 activity. These activities show that for very small differences in structures, there are very large differences in their activities. Due to this, it is unclear as to how such activities can be linked to the treatment of diseases/conditions without being directly tested for such activity.

The amount of direction or guidance present: The guidance present in the specification is that of the compounds that any compounds having such NHE-1 inhibitory activity will treat any disease/condition that has been linked to this NHE-1 receptor. These diseases/conditions range from cytotoxic therapy to over excitability of the CNS to high blood pressure. The specification states that NHE-1 receptors have been linked to many different activities of the body and therefore play a role in a wide variety of diseases/condition. However, there are no examples of the instantly claimed compounds (or other compounds having the same NHE-1 receptor activity) actively treating a disease/condition. The specification does not seem to enable a correlation between the mediation of NHE-1 receptors and the treatment of any and all diseases.

The breadth of the claims: The claims are drawn to the treatment and prevention of any and all diseases mediated by the NHE-1 receptor with the compound of claim 1.

The quantity of experimentation needed: The quantity of experimentation needed is undue. One skilled in the art would need to determine what diseases out of all known diseases would be benefited by the mediation of NHE-1 receptors and then would further need to determine which of the claimed compounds would provide treatment of the disease.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compounds of claim 1 for the treatment of any disease. As a result necessitating one of ordinary skill to perform an exhaustive search for which diseases can be treated by which compound of claim 1 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, one of ordinary skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compounds of the instant claims, with no assurance of success.

This rejection can be overcome by deleting the claims.

Applicant argues that the claims are directed to treating specific diseases. Those diseases are (as claimed) treatment of cardiovascular disease, metabolic disease, cancerous disease, fibrotic disease,

acute or chronic damage to, or disorders or indirect sequelae of organs and tissues caused by ischemic or reperfusion events;

arrhythmias, life-threatening cardiac ventricular fibrillation, myocardial infarction, angina pectoris;

ischemic states of the heart, ischemic states of the peripheral and central nervous system, stroke, cerebral oedema attack, ischemic states of peripheral organs and tissues;

states of shock;

diseases in which cellular proliferation represents a primary or secondary cause;

cancer, metastasis, prostate hypertrophy, prostate hyperplasia;

atherosclerosis, disturbances of lipid metabolism, high blood pressure;

disorders of the central nervous system;

non-insulin-dependent diabetes mellitus, late damage from diabetes;

thromboses, disorders resulting from endothelial dysfunction, intermittent claudication;

fibrotic disorders of internal organs, fibrotic disorders of the liver, fibrotic disorders of th kidney, fibrotic disorders of vessels, fibrotic disorders of lung, fibrotic disorders of the heart;

heart failure, congestive heart failure, acute or chronic inflammatory disorders, disorder caused by protozoa;

malaria, or coccidiosis in poultry, comprising administering to a patient in need thereof, allergic shock, cardiogenic shock, hypovolaemic shock, bacterial shock, essential hypertension, disorders resulting from over excitability of the CNS, epilepsy ore centrally induced convulsions, anxiety states, depressions, psychoses, protecting an organ in transplant, protecting a removed organ during or in storage, preventing age-related tissue change, prolonging life, reduction of cardiotoxic effects in thyrotoxicosis, acute or chronic damage, life-threatening cardiac ventricular fibrillation, metastasis, fibrotic disorders of the heart, heart failure, congestive heart failure, treatment of a disease related to NHE and protecting the organs or blood vessels during surgical intervention. Specifically, claims 44, 46, 62 and 63 are drawn to treatment of a disease related to NHE or NHE1. This is not claiming specific diseases to be treated. Applicant refers to page 8 lines 19-32 for support enablement of the rejected claims. However, this part of the specification refers to what might be treated by NHE inhibitors.

Applicant argues that the specification provides more than a reasonable correlation to the scope of the claims. Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of

potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, although drawn specifically to cancer cells, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with

characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Applicant argues that what is well known in the art should be omitted. However, the treatment of cancer is not well known in the art (as shown above). The treatment of acute or chronic damage (from what) or the prevention of age-related tissue change or the prolonging live in a patient is not well known in the art. Due to this, such need much more support that is currently in the specification.

Lastly, applicants argue that all compounds encompassed by the instant claim 1 are not required to be exemplified. That is true. However, the instant claims are being rejected due to enablement for the use of the compounds to treat/prevent /prolong life and not the compounds and the method of making

the compounds, namely claims 1-6, 8 and 49. Only the method of treatment of the above listed conditions is being rejected.

Allowable Subject Matter

2. Claims 1-6, 8 and 49 are free of prior art.

Conclusion

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. Margaret Seaman whose telephone

number is 571-272-0694. The examiner can normally be reached on 730am-4pm, Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thomas McKenzie can be reached on 571-272-0670. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D. Margaret Seaman
Primary Examiner
Art Unit 1625

dms